



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: August 26, 2005

To: NCCTG Primary Clinical Research Associates

From: Janis Gjervik
Protocol Development Coordinator

Re: N0321, Phase I/II Study of PS-341 in Combination with Paclitaxel, Carboplatin, and Concurrent Thoracic Radiation Therapy for Non-small Cell Lung Cancer (NSCLC)

The purpose of this memorandum is to provide investigators with a recent report of an adverse event that has occurred in association with PS-341 for a study where the Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI) is distributing this agent. You may have also received this communication directly from DCTD.

AE_1938801

Please note that all risks currently cited in the NCCTG consent form cannot be omitted; it is at the discretion of your local IRB as to whether they wish to add risks based on the enclosed information. If a determination has been made by the NCCTG Research Base that a protocol amendment is necessary, you will receive the NCI-approved protocol addendum at a later date; for purposes of cross-reference, this communication will cite the adverse event noted above.

Please submit this adverse event to your Institutional Review Board.

If you have any questions concerning this communication, please contact Janis Gjervik at 507/284-4852.

JG
enclosure



DATE: July 27, 2005

FROM: J. Wright, M.D., Ph.D., Investigational Drug Branch, CTEP, DCTD, NCI
S. Percy Ivy, M.D., Investigational Drug Branch, CTEP, DCTD, NCI

SUBJECT: PS-341 (bortezomib)/17-Allylaminogeldanamycin (17-AAG) IND Safety Report,
AE# 1938801

TO: Investigators of NCI-sponsored Trials Using PS-341 (IND 58443) and 17-AAG
(IND 57966)

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies conducted under a U.S. IND to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. Please find attached a copy of an IND Safety Report recently submitted to the FDA for the CTEP-sponsored investigational agents PS-341 (IND 58443) and 17-AAG (IND 57966).

Please complete the following:

- Send a copy of the IND Safety Report to your Institutional Review Board (IRB) according to your local IRB's policies and procedures.
- File a copy of the IND Safety Report in your protocol file.

Please note that for Cooperative Group studies, the Cooperative Group Operations Office will provide instructions for IRB submissions, any patient notifications, etc.

CTEP's evaluation of this IND Safety Report in light of previous experience with PS-341 and 17-AAG does not require a change in the clinical protocols for this agent at this time.

Please continue to report events according to the adverse event reporting guidelines in your protocol(s).

The Adverse Events Assessment that describes the following adverse events, previous experience under this IND, and the total number of patients enrolled under this IND is attached:

A 69-year-old male with acute myeloid leukemia (AML) experienced hypertension, febrile neutropenia, hyperglycemia, and ultimately died from a CNS hemorrhage while on a phase 1 trial using the investigational agents PS-341 and 17-AAG.

ADVERSE EVENTS ASSESSMENT

IND	58443	ADVERSE EXPERIENCE REPORT NO. #43
NSC	681239	IND Safety Report:
PS-341 (bortezomib; Velcade™)		Event: Gr. 5: CNS Hemorrhage
IND	57966	Gr. 4: Glucose (hyperglycemia)
NSC	330507	Gr. 3: Febrile neutropenia
17-Allylaminogeldanamycin (17-AAG)		Gr. 3: Hypertension
AE:	1938801	Protocol: 6520

The patient was a 69-year-old male with acute myeloid leukemia (AML) who experienced hypertension, febrile neutropenia, hyperglycemia, and ultimately died from a CNS hemorrhage while on a phase 1 trial using the investigational agents PS-341 and 17-allylaminogeldanamycin (17-AAG). He began his first course of treatment on June 14, 2005 receiving 17-AAG 150 mg/m² IV over 60 minutes on days 1, 4, 8, and 11 and PS-341 0.7 mg/m² IV over 3-5 seconds on days 4, 8, and 11 during a 21-day cycle. He received his last dose of PS-341 and 17-AAG on June 24, 2005 (Cycle 1, Day 11).

The patient was initially diagnosed with chronic lymphocytic leukemia (CLL) in 1999 and treated with fludarabine and rituximab. Post-treatment, he had continued pancytopenia and was diagnosed with myelodysplastic syndrome, which transformed clinically into a therapy-related AML in March 2005. He underwent induction with daunorubicin and cytarabine on April 4, 2005; however, his subsequent bone marrow biopsies revealed persistent AML.

On June 13, 2005, he was admitted to the hospital for 17-AAG and PS-341 therapy, which he began the next day. Of note, the patient had baseline grade 3/4 thrombocytopenia. His hospital course was complicated by febrile neutropenia, thrombocytopenia, anorexia, diarrhea, nausea, and vomiting for which he was treated with broad spectrum antibiotics (including tobramycin and antifungal agents), IV fluids, and antiemetic therapy (including Ativan®, Zofran®, transdermal scopolamine, and Phenergan®). He also developed mental status changes while receiving therapy that waxed and waned. In the late evening of June 21, 2005, the patient had worsening confusion and apparently fell in his room. A CT scan of the head performed on June 22, 2005 was unremarkable, and the confusion was attributed to the Phenergan®, which was then stopped. Within 24 hours of Phenergan® termination, the confusion had completely resolved (June 24, 2005). On the morning of June 25, 2005, the patient was afebrile, alert, and oriented, with no focal deficits or confusion. With negative blood cultures and a slight increase in his creatinine level to a nadir of 1.89 mg/dL (reference range: 0.9-1.3 mg/dL), tobramycin and Flagyl® were withheld, and his IV fluids were increased. Although his systolic blood pressure was elevated at 170-180 mm Hg, no medical intervention was done. He received a platelet transfusion for a count of 8 K/μL (reference range: 150-400 K/μL), which then increased to 44 K/μL. He also developed hyperglycemia with a glucose level of 371 mg/dL (reference range: 74-106 mg/dL) and was treated with insulin. The patient reported some visual changes at 11:45 am. He also began vomiting, which continued throughout the day, and received antiemetics. Of note, the patient had one episode of mild hematemesis and bright red blood per rectum that day. By approximately 6:30 pm, his glucose level had risen to 436 mg/dL, and he received continuous insulin coverage. Although his mental status at midnight was reported to be the best it was all day, within several hours, it had significantly declined. Concomitantly, worsening of his systolic blood pressure (200-210 mg Hg) and declining respiratory function, manifesting as minimal respiratory effort and, eventually, Cheyne-Stokes respirations, was noted. He received another platelet transfusion at 2:30 am due to a platelet count of 19 K/μL. At 6:20 am, the patient was endotracheally intubated for impending respiratory collapse and transferred to the ICU. An emergency CT scan of the head revealed a large midline posterior fossa intraparenchymal cerebellar hemorrhage with significant regional mass effect. A Neurology consult was significant for fixed pupils and negative cranial nerve reflexes. After consultation with the family, the patient was given a "do not resuscitate status" and expired at 5:03 pm on June 26, 2005.

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An autopsy was conducted on June 27, 2005 and revealed a fatal intraparenchymal brain hemorrhage felt to be due to hypertension and thrombocytopenia in the setting of refractory leukemia. There was evidence of chronic hypertension as demonstrated by concentric left ventricular hypertrophy, but no evidence of head trauma at autopsy.

The patient's past medical history is significant for CLL, pancytopenia, myelodysplastic syndrome, and hypertension as stated above. Medications at the time of death included broad spectrum antibiotics, Ativan[®], Zofran[®], transdermal scopolamine, and insulin.

The incidences of CNS hemorrhage, hyperglycemia, febrile neutropenia, and hypertension reported to the NCI as serious adverse events under the PS-341 and 17-AAG INDs with attributions to the study agents are as follows:

Adverse Event	PS-341	17-AAG
CNS Hemorrhage	n = 3 2 Possible, 1 Unlikely	n = 0
Hemorrhage - other	n = 8 2 Possible, 4 Unlikely, 2 Unrelated	n = 0
Glucose (hyperglycemia)	n = 10 3 Possible, 6 Unlikely, 1 Unrelated	n = 9 2 Possible, 2 Unlikely, 5 Unrelated
Febrile neutropenia	n = 10 4 Possible, 5 Unlikely, 1 Unrelated	n = 5 2 Possible, 3 Unlikely
Hypertension	n = 2 1 Possible, 1 Unrelated	n = 0

In this case, it is felt that the CNS hemorrhage, hyperglycemia, and febrile neutropenia were possibly related to both 17-AAG and PS-341. Although there was no evidence of head trauma at autopsy, the possibility of bleeding related to the fall cannot be excluded. Hypertension is considered unlikely to be related to the investigational agents.

There have been a total of 1,444 patients enrolled in NCI-sponsored clinical trials under IND 58443 (PS-341) and 381 patients enrolled in NCI-sponsored clinical trials under IND 57966 (17-AAG).

	CNS hemorrhage	Glucose (hyperglycemia)	Febrile Neutropenia	Hypertension
17-AAG	Possible	Possible	Possible	Unlikely
PS-341	Possible	Probable	Possible	Unlikely
Acute myeloid leukemia	Probable	Unlikely	Possible	Unlikely
Thrombocytopenia	Probable	Unlikely	Unlikely	Unlikely
Trauma w/ CNS hemorrhage	Possible	Unlikely	Unlikely	Probable

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Date: 7/29/05

Signature: John Wright M.D.
John Wright, M.D., Ph.D.
(IDB Monitor for PS-341)

Date: 07.29.05

Signature: Percy Ivy
Percy Ivy, M.D.
(IDB Monitor for 17-AAG)

If this assessment is changed, we will notify your office.

cc: Jean-Claude Tetreault & productsafety@mpi.com
Millennium Pharmaceuticals, Inc.

Helen Street
Kosan Biosciences, Inc.